Original Article

Comparison of the Efficacy of Medical Expulsive Therapy for the Treatment of Distal Ureteric Stones with and without Mirabegron

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ABSTRACT

OBJECTIVE: To compare the efficacy of expulsive medical therapy for treating ureteric stones with or without mirabegron as an add-on to Diclofenac.

METHODOLOGY: A prospective randomized controlled trial was undertaken between April 2018 to March 2019 at the Asian Institute of Medical Sciences, Hyderabad, Sindh. A total of two hundred participants who had ureteric stones were enrolled using non-probability convenience sampling. Diclofenac Only 100 mg/day (group A, n=100), and Mirabegron 50 milligrams/day + diclofenac 100 milligrams/day (group B, n=100) were administered to patients, adjunctively. Age, sex, site, size of the stone, and laterality were noted. The stone expulsion time for each patient was evaluated. SPSS version 24 was used for analysis. A p-value of 0.05 or less was set as the cut-off value for significance.

RESULTS: Age, sex, site of stone, and laterality were not significantly different between the two groups (p=0.886, p=0.755, p=0.168, p=0.321, & p=0.889, respectively). Spontaneous stone expulsion ratios were observed as 43% and 71% in group A and group B (p<0.0001), respectively. However, no statistically significant association was found between mirabegron and the stone expulsion time (p=0.667). Group B showed a significantly higher stone expulsion rate in patients with stone size >4mm (p=0.04). The SER for middle and distally localized stones was higher in group B with a statistically significant p=0.02.

CONCLUSION: The present study indicated that combined therapy with both mirabegron and Diclofenac is more effective than monotherapy with Diclofenac only. Mirabegron is a safe drug that improves the stone expulsion ratio in ureteric stones by > 4mm.

KEYWORDS: Mirabegron, Ureteric stone, Colic, Medical Expulsive Therapy, Efficacy, Diclofenac

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INTRODUCTION

The ureter is responsible for carrying urine from the kidneys to the urinary bladder. It is a tubular structure lined by urothelium, a transitional epithelium capable of dilating upon stimulation[1]. The muscle layer of the ureter functions continuously with peristalsis under the autonomous stimulation of the Cajal cells at the ureteropelvic junction. Many receptors and neurotransmitters are found in the ureteral muscles that facilitate contraction and relaxation[2]. One of the primary receptors present in both the ureters and urinary bladder is the β-3 adrenoceptors, which cause relaxation of the smooth muscles of the ureters. Passage of a ureteric calculi through the ureter can be facilitated by blocking the contracting pathways or stimulating the relaxation cascade[3-5].

The role of β-3 adrenergic receptor agonists in the relaxation of the detrusor smooth muscle of the urinary bladder is well-established, which helps to enhance the capacity of the bladder during the bladder storage phase without adversely affecting the voiding determinants, such as Qmax-the maximum flow rate of urine, the pressure of detrusor/bladder at Qmax (PdetQmax), and residual urine volume[6].

Mirabegron, a beta-3 adrenergic receptor agonist, has shown excellent results in patients suffering from overactive bladder (OAB) syndrome, successfully restoring the bladder function to its full potential[7-9]. Recent advancements have revealed that mirabegron can be used adjunctively with other alpha-adrenoceptor blockers and calcium antagonists in expulsive medical therapy in individuals with urolithiasis[2,10].

Medical expulsive therapy (MET) is a treatment modality where certain medications are administered to patients. It helps in the spontaneous expulsion of the stones[11]. It is being preferred over surgery and is being used widely worldwide. Drugs including alpha-adrenoceptor antagonists, calcium antagonists, phosphodiesterase (PDE) inhibitors, and spasmolytics have been shown effective in randomized clinical trials to treat urolithiasis[12].

A plethora of research into this field has recently emerged to find a drug that will increase the stone expulsion ratio, reduce the time for stone expulsion, and relieve the patient of pain. However, the previous studies have been inconsistent in evaluating the

clinical outcome of the MET, and most of the past studies are riddled with bias and confounding factors[10-13]. Therefore, the present study was undertaken to determine the efficacy of mirabegron when given in combination with Diclofenac in patients with complaints of urolithiasis.

METHODOLOGY

A prospective randomized controlled trial was performed at the Department of Urology, Asian Institute of Medical Sciences, Hyderabad, Sindh, from April 2018 to March 2019. The ethical approval was obtained from the Institutional Review Board (IRB) committee before the study. A total of 200 patients participated in the study after all participants had secured informed consent. The non-probability convenience sampling technique was applied to enroll participants in the study. All patients with ureteric stones ≤10 millimeters, located in the upper, middle, or lower ureter were eligible to partake in the study. Patients with severe hydronephrosis, infection, pregnancy, structural renal anomalies, benign prostate hyperplasia, and poorly controlled hypertension were excluded from the study.

Diclofenac 100mg/day was administered to the initial hundred participants, followed by the subsequent hundred patients administered mirabegron 50mg/day and Diclofenac 100mg/day, adjunctively. Detailed patient history and general physical examination followed by laboratory assessments including the electrolyte tests, urine DR, and urine C/S. The ureteral stones were diagnosed using a kidney-ureter-bladder (KUB) X-ray and renal ultrasound. A computed tomography (CT) scan was performed on suspected patients. The clinical variables were recorded, including the patient's age, gender, size of the ureteral stone, and laterality.

Patients were advised to visit the out-patients department every five days. At follow-up, the participants were inquired about the passing of the ureteric stone; the waiting period should not be more than 4 weeks[15]. The drugs' mild or severe adverse effects were observed and recorded, and spontaneous stone expulsion times and the stone expulsion ratio (SER) were recorded.

The statistical Package for Social Sciences version 24 was utilized for data analysis. Continuous data were expressed as mean and standard deviation, while categorical data were expressed as frequency or percentage. A Chi-square test was used to compare the two treatment groups. A p-value equal to or less than 0.05 was set as the cut-off value for significance.

RESULTS

A total of 200 patients with a mean age ± SD of 28.7±8.2 years in group A (Diclofenac only) and 28.8±6.4 years in group B (Diclofenac + Mirabegron) participated in the study. Overall, 113 (56.5%) male patients and 87 (43.5%) female patients were enrolled. The average size of ureteral stone in Group A (Diclofenac only) was 6.5±1.5 mm, while that of Group B (Diclofenac + Mirabegron) was 6.7±1.5 mm. (Table I).

TABLE I: SOCIODEMOGRAPHIC AND CLINICOPATHOLOGICAL PROFILE OF PATIENTS IN THE STUDY (n=200)

	Group A (Diclofenac Only)	Group B (Diclofenac+Mirabegron)	p-value
Mean Age ± SD	28.7±8.2 years	28.8±6.4 years	0.886
Gender n(%)			
Male	56	57	0.755
Female	44	43	
Stone (mm)	6.5±1.5	6.7±1.5	0.611
< 4 mm	29/100	17/100	
> 4 mm	71/100	83/100	0.043
Laterality n (%)			
Left	51	45	0.321
Right	49	55	
Stone Location n(%)			
lower ureteric stone	41	40	0.889
mid-ureteric stone	41	44	
upper ureteric stone	18	16	

In group A, 41% were localized at the lower ureter, 41% were at the middle ureter, and 18% were upper ureter. In group B, a similar pattern was observed (p-value=0.889). (Table I). Lower ureteric stones were smaller than the middle and upper ureteric stones; however, stratification was not done according to stone size in different locations.

The stone expulsion ratio (SER) for group A was 43%, while that of group B was 71%, with a significant p-value of <0.0001 (Figure I). The Chi-square test was applied to assess whether there was any statistically significant difference between the groups concerning the stone expulsion rate and size of the stone. It was found that, in group A, 31 (72.09%) patients with a stone larger than 4 mm were expelled, while in Group B, 62 (87.32%) patients had stone expulsion with a stone size of >4mm (p=0.042). The stone expulsion time for group A was 10.2±3.2 days, while in group B, it was 10.3±3.4 days. However, no significant difference was noted (p-value=0.667). (Table II).

In group A (Diclofenac only), it was observed that the SER for upper ureteric stone was only 7%, for a mid-ureteric stone, it was 16%, and for lower ureteric stone, the SER was 19%. In group B (Diclofenac + Mirabegron), the SER for upper ureteric stone was 8%, for middle and distally localized stones, it was 32% each, respectively, with a statistically significant p-value of 0.02. (Figure II).

FIGURE I: SPONTANEOUS STONE EXPULSION RATIO (SER) IN GROUP A AND GROUP B (n=200)

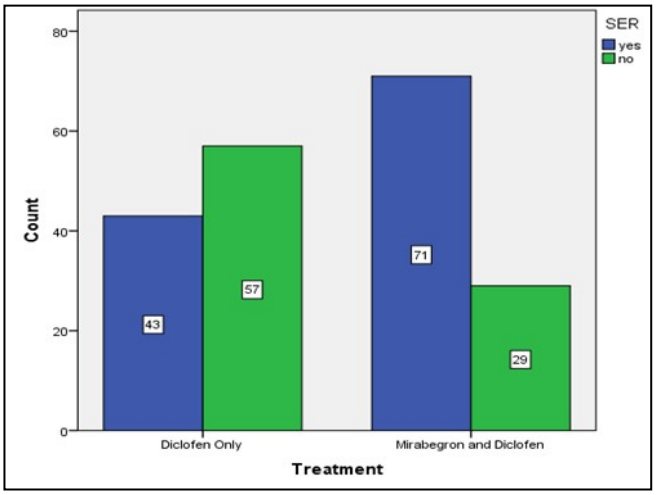
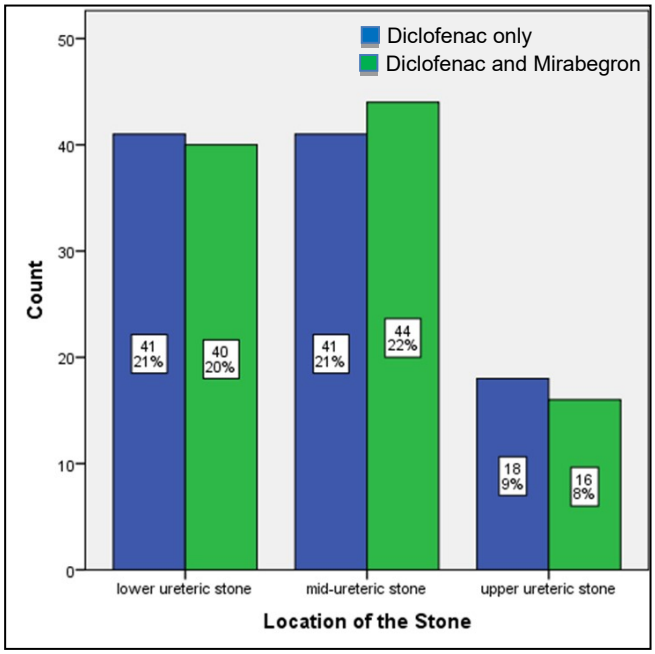


TABLE II: FOLLOW-UP ASSESSMENT OF BOTH TREATMENT GROUPS (n=200)

	Group A (Diclofenac Only)	Group B (Diclofenac +Mirabegron)	p - value
Stone expulsion ratio			
Overall, n (%)	43	71	<0.0001*
≤4 mm	12 (27.91%)	09 (12.68%)	
>4 mm	31 (72.09%)	62 (87.32%)	0.042
Stone expulsion time (day)	10.2±3.2	10.3±3.4	0.667

**p<0.05 is statistically significant.*

FIGURE II: RELATIONSHIP BETWEEN THE SITE OF STONE & STONE EXPULSION RATIO IN GROUP A AND B



DISCUSSION

Ureteral stones can cause irritability, urinary urgency, and frequency and mimic overactive bladder syndrome. Medical expulsive therapy aims to decrease symptoms and enhance spontaneous expulsion ratio (SER) with the help of alpha adrenoreceptor antagonists and antimuscarinic medicines. Mirabegron is an antimuscarinic agent which activates the beta-3 adrenergic receptors in the urinary bladder, inducing its relaxation[15,4]. Mirabegron is remarkably effective against overactive bladder syndrome and has lesser adverse effects, such as increased heart rate, unstable blood pressure, and dry mouth[16].

More recently, the efficacy of mirabegron is being investigated in expulsive medical therapy (MET), a more effective therapy for treating ureteric calculi, most commonly those in lower ureteral locations. Spontaneous expulsion depends on certain variables like the size of the stone, site, smooth muscles spasms, edema in the ureter, and anatomical features of the ureter[17,18].

In the present study, we evaluated the efficacy of Diclofenac in combination with mirabegron compared to when Diclofenac is given alone in expulsive medical therapy. It was revealed that patients treated with both drugs had a significantly better clinical outcome with a higher spontaneous expulsion ratio (SER) of intramural ureteral stones. Upon comparison, the overall SER for group A was 43 out of 100, while for group B, it was 71 out of 100 (p-value=0.000). Group A's mean stone expulsion time was 10.2±3.2 days, while group B 10.3±3.4 days. Albeit, not significantly different (p-value=0.667).

Our findings are in accordance with recent studies. In one such study by Solakhan M 2019[17], a spontaneous expulsion ratio (SER) of 73.5% was reported in patients given mirabegron in adjunct to Diclofenac, and a much lower SER of 47.1% was reported in the control group (p-value=0.026). Similarly, they did not find any significant difference in stone expulsion time (p-value=0.979).

In the current study, spontaneous expulsion ratio (SER) for patients with ≤ 4 mm stones were reported as 12% in group A while 9% in group B. The SER for stones larger than 4mm for group B was higher, i.e., 62 (87.32%), than group A, i.e., 31%. It was statistically significant (p-value=0.04).

In a randomized multicenter study by Bayar G. et al. [18], the efficacy of mirabegron and silodosin was evaluated. They evaluated the patients with stone sizes between 4-10 mm. In contrast to our study, they reported that the stone expulsion rate was similar among all groups. They also claimed that mirabegron had no significant role in stone expulsion time (p-value>0.05). However, the analgesia requirement was lower in the group prescribed mirabegron 50mg per

day in patients with distal ureteric stones (p-value=0.004) or stones larger or equal to 6 mm (p-value=0.017) compared to the control group.

In the present study, patients were under observation for any side effects of the drug. No significant changes in blood pressure or heart rate were reported. A review of the literature supports our findings, revealing that a 50 mg dose of mirabegron is not correlated with disturbance in the blood pressure, QT prolongation, or increased heart rate[19]. In contrast, the drug's 100-200 mg dose was linked significantly with arrhythmias. Other studies reported that other anticholinergics were associated with a greater risk of dry mouth and stomach upset than mirabegron. Additionally, mirabegron works via a completely different pathway without manipulating the voiding phase[19].

Substantial evidence has shown that administration of mirabegron for the treatment of distally localized ureteral stones, adjunctively with other α-adrenoreceptor antagonists, is associated with improved SER, reduced stone expulsion interval, and reduced colic attacks[21-24].

Similarly, in the present study, it was observed that the group B had not only the overall greater SER of 71% compared to the 43% in group A (p-value<0.0001), the SER for the middle and lower ureteral stones was significantly higher as compared to upper ureteric stones (p-value=0.02).

CONCLUSION

Mirabegron given adjunctively with Diclofenac has shown to be safe and effective in treating ureteric stones with increased stone expulsion ratio and no reported side effects. Further research is needed to highlight the various aspects of mirabegron as an agent commonly used in expulsive medical therapy.

Ethical permission: Asian Institute of Medical Sciences ERC letter No. AIMS/ERCL/6304/18, dated 28-3-2018.

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AUTHOR CONTRIBUTIONS

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Memon II:	Statistical analysis
Soomro KQ:	Drafting
Hussain SA:	Data collection
Mughal SA:	Data collection
Soomro N:	Data compiling

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